traceptives, the rate increased more than sevenfold; and in those women who both smoked heavily and used oral contraceptives the rate increased at least twentyfold.

Carbon Monoxide

A study of male and female office workers found no sex difference in the relationship between carboxyhemoglobin (COHb) levels and daily consumption of cigarettes. However, women smoked fewer cigarettes on the average than men. The study found that the COHb levels in smokers were higher among the sedentary office workers than among physically active meat porters and that both had higher levels of COHb than pregnant women who smoked (12). The latter had COHb levels approximately three times higher than that of nonsmokers. Wald reported from a cross-sectional study that carboxyhemoglobin levels of smokers are a better indicator of the risk of atherosclerotic cardiovascular disease than a reported smoking history (48). The proportion of both men and women with atherosclerotic disease increased with increasing levels of COHb.

Comment

Women are less likely to experience a myocardial infarction than men. Nevertheless, coronary heart disease is still a leading cause of death and disability in women. The lower mortality rates from acute myocardial infarction and chronic ischemic heart disease of women as compared to men are paralleled by less extensive and severe atherosclerosis in the coronary artieries of adult women. The severity of aortic atherosclerosis, however, is about the same in both sexes.

The relationship of cigarette smoking to atherosclerosis, heart attack,and other ischemic diseases secondary to atherosclerosis has not been studied among women as extensively as among men; moreover, most studies have been limited to white women. It is not known whether atherosclerotic plaques observed at autopsy are more extensive and severe in women smokers than in nonsmokers. No data are available concerning the incidence of death from atherosclerotic aneurysms of the aorta among women who smoke relative to those who do not, and inadequate data exist to indicate whether cessation of smoking by women is associated with a beneficial reduction in the risk of heart attack, as has been demonstrated in men. The effect of smoking on the threshold for the onset of angina pectoris and on cardiac function in women with coronary heart disease has not been studied.

Nevertheless, compelling data from prospective cohort studies and from case control investigations indicate that cigarette smoking is a major risk factor for fatal and nonfatal heart attacks in women. In general, cigarette smoking increases the risk by a factor of about two, and in younger women cigarette smoking may increase the risk several fold. Women who smoke low-"tar" and low-nicotine cigarettes have a greater risk of suffering heart attacks than nonsmokers but appear to have a smaller risk than women smoking moderate-to-high "tar" and nicotine products.

Smoking is a major risk factor for arteriosclerotic peripheral vascular disease in women, as it is in men. For both men and women the successful outcome of surgical repair of this disorder is enhanced by cessation of smoking. Smoking is a major risk factor for subarachnoid hemorrhage and for the development of malignant hypertension. Smoking is reported to depress the natural relative elevation of high-density lipoprotein cholesterol enjoyed by women. In women who use oral contraceptives, smoking is a powerful synergistic risk factor for subarachnoid hemorrhage and for myocardial infarction.

While data implicating smoking as a risk factor for various cardiovascular diseases in women are neither as extensive nor as complete as for men, the evidence nonetheless clearly establishes cigarette smoking as a major correlate for myocardial infarction, arteriosclerotic peripheral vascular disease and subarachnoid hemorrhage in women (45).

Summary

Coronary heart disease is the major cause of death among both males and females in the U.S. population. The 1979 Surgeon General's Report clearly demonstrated the close association of cigarette smoking and increased coronary heart disease among males. This report reviews the evidence associating cigarette smoking and cardiovascular disease in women:

1. Coronary heart disease, including acute myocardial infarction and chronic ischemic heart disease, occurs more frequently in women who smoke. In general, cigarette smoking increases the risk by a factor of about two, and in younger women cigarette smoking may increase the risk several fold.
2. Cigarette smoking is a major independent risk factor for coronary heart disease in women; it also acts synergistically with other coronary heart disease risk factors producing a risk greater than the sum of the individual risks.
3. The use of oral contraceptives by women cigarette smokers

increases the risk of a myocardial infarction by a factor of approximately ten.

4. Women who smoke low "tar" and nicotine cigarettes experience less risk for coronary heart disease than women who smoke high "tar" and nicotine cigarettes, but their risk is still considerably greater than that of nonsmokers.

5. Increased levels of high-density lipoprotein (HDL) are correlated with a reduced risk for an acute myocardial infarction; women cigarette smokers have decreased levels of HDL.

6. Cigarette smoking is a major, independent risk factor for the development of arteriosclerotic peripheral vascular disease in women. Smoking cessation improves the prognosis of the disorder and has a favorable impact on vascular patency following reconstructive surgery.

7. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage; the use of both cigarettes and oral contraceptives appears to increase synergistically the risk for subarachnoid hemorrhage.

8. Women who smoke cigarettes may be more likely to develop severe or malignant hypertension than nonsmoking women.

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CANCER.

CANCER

Introduction

For more than 40 years cancer has been second only to cardiovascular disease as a cause of death in the United States. With the exception of the very elderly, the death rate for adult men exceeds that for adult women for both groups of diseases, implying a difference in genetic susceptibility, environmental exposures or lifestyles between the sexes, or a combination of genetic and environmental factors.

Placing these generalizations about cause of death in perspective, current data from the National Center for Health Statistics (28) reveal the following statistics:

There are 105 male births each year in the United States for every 100 female births, but the higher death rate for males results in a ratio of 100 men to 100 women at ages 20 to 24 and of 79:100 at ages 65 to 69, and of 47:100 at age 85. Life expectancy in the United States in 1976 was 68.7 years for males compared to 76.1 years for females.

Heart disease and cancer currently account for 60 percent of deaths in the United States. In contrast to the decline in the age-adjusted death rates for ischemic heart disease, the age-adjusted death rate for cancer has increased. Hidden in this small rise in the overall cancer statistics is a remarkable increase—a veritable epidemic—of cancer of the lung in both men and women. In the past quarter century, deaths from cancer of the respiratory tract tripled in the white population and quadrupled in the black population. The remarkable male-to-female preponderence of lung cancer in the 1940s and 1950s has been decreasing in the 1960s and 1970s; the rate of increase in lung cancer in males is slowing while the rate of increase of lung cancer in females is accelerating. As a cause of death, lung cancer in women is now second only to mammary carcinoma and will likely displace breast cancer as the leading cause of cancer mortality in women in the 1980s (1) (see Figure 1).

The 1964 Surgeon General's Report reached the following conclusion: "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effects of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction" (33). Since then, a number of retrospective and prospective epidemiologic studies, experimental animal carcinogenesis studies, and studies of human tissues at surgery and autopsy have confirmed and extended those conclusions. Cigarette smoking is the major cause of cancer of the lung in women. The risk increases with the number of years the individual smoked, the number of ciga-

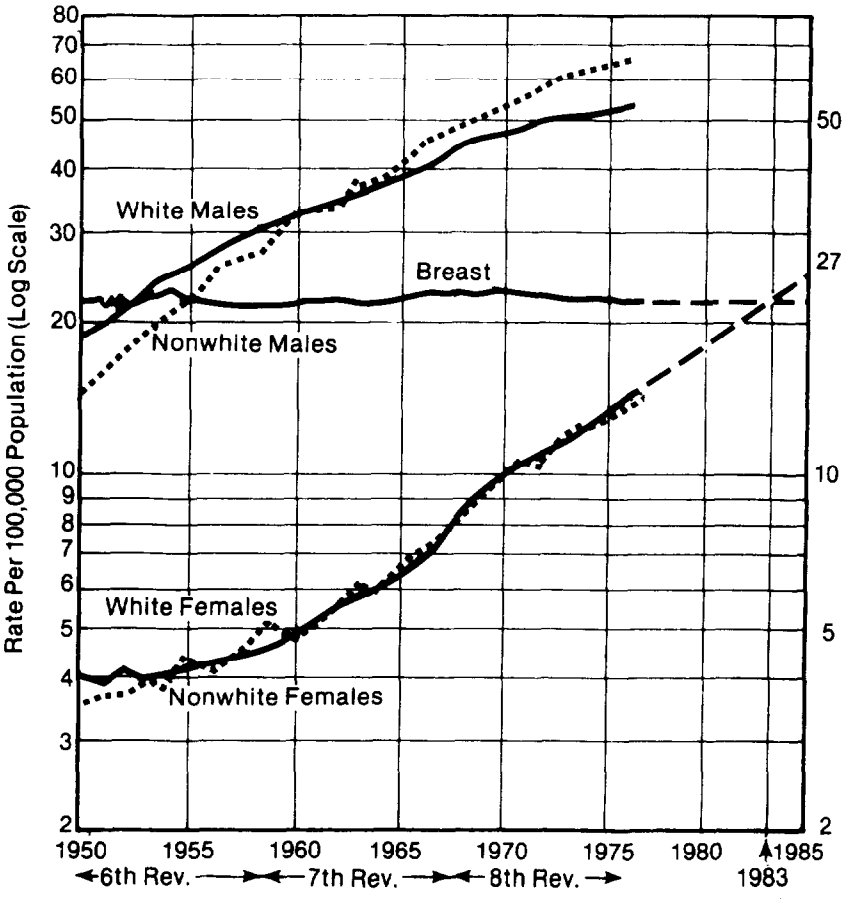

FIGURE 1.—Age-adjusted death rates* for malignant neoplasm of trachea, bronchus and lung, by color and sex compared to rates for malignant breast neoplasm, United States, 1950–1977; projection for white females to 1985.*****

*Adjusted by the direct method to the U.S. population, 1940.
**ICD 6th and 7th Rev. Nos. 162, 163 and 8th Rev. No. 162.
***Projection based on average annual rate of increase over last 10 years.
SOURCE: National Cancer Institute (25), National Center for Health Statistics (27).

rettes smoked, the "tar" and nicotine level of the cigarette smoked and the degree of inhalation, and is inversely related to the age at which the individual began smoking, being higher for those who begin smoking at younger ages. The risk of developing

cancer is diminished significantly by quitting smoking and is lessened somewhat by switching to low-tar, low-nicotine filter-tip cigarettes (43,45). Considerable evidence has also shown that cigarette smoking is a significant cause—for women and men—of cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas. Much of this information has been summarized in previous issues of "The Health Consequences of Smoking" or the Surgeon General's Reports (33–43).

Table 1 lists the new cases and deaths estimated to occur in 1980 for those cancers which are causally associated with cigarette smoking (1). Smoking will contribute to 43 percent of the male and 18 percent of the female newly diagnosed cancer cases in the United States in 1980 and to 51 percent of the male and 26 percent of the female cancer deaths. This table does not imply that cigarette smoking causes each of these individual cancers. It does, however, identify the impact of cigarette smoking on the major cancers now known to be associated with cigarette smoking. Most of the cases of cancer of the lung and larynx could have been prevented, as could a substantial proportion of the cancer deaths at the other sites listed.

In this chapter, selected data on cancer and smoking among women will be reviewed and summarized. Where necessary for clarity, data previously reported will be summarized briefly.

Lung

The lung is a complex organ lined by at least five types of epithelial cells, each of which theoretically might give rise to one or more types of neoplasm. In addition to the epithelial cells, blood vessels and connective tissue are prominent in the lungs. Both visceral and parietal portions of the lung are covered by synovial membranes, which also are subject to neoplastic transformation. The World Health Organization's classification of malignant tumors (Table 2) includes multiple histologic types, of which epidermoid, small cell, adenocarcinoma, and large cell carcinoma are causally related to cigarette smoking and display significant dose-response relationships in epidemiologic studies (7,43). These four tumors are the most common histologic types of lung cancer in both men and women. However, there are differences in the distribution of the different types of lung cancer in men and women and in smokers and nonsmokers. Epidermoid carcinoma was the most common histologic type of lung cancer in the male smoker, while adenocarcinoma was most common in the female smoker and in nonsmokers of both sexes in a series recently published from the Mayo Clinic (Table 3) (31).

TABLE 1.—Estimated new cancer cases and deaths for sites associated with cigarette smoking, 1980

Site	Estimated New Cases			Estimated Deaths		
	Total	Male	Female	Total	Male	Female
All Sites	785,000*	387,000*	398,000*	405,000	219,500	185,500
Lung	117,000	85,000	32,000	101,300	74,800	26,500
Pancreas	24,000	12,500	11,500	20,900	11,100	9,800
Urinary Bladder	35,500	26,000	9,500	10,300	7,000	3,300
Oral	25,500	17,900	7,600	8,800	6,100	2,700
Kidney & Other Urinary	16,900	10,500	6,400	7,900	4,800	3,100
Esophagus	8,800	6,200	2,600	7,600	5,500	2,100
Larynx	10,700	9,000	1,700	3,500	2,900	600
All Tobacco Related	238,400	167,100	71,300	160,300	112,200	48,100

*Carcinoma *in situ* is not included. There are 45,000 new cases of uterine cervical carcinoma *in situ* each year. Non-melanoma skin cancer is not included. Approximately 400,000 new cases of non-melanoma skin cancer occur annually.
SOURCE: American Cancer Society (1).

TABLE 2.—World Health Organization classification of malignant pleuro-pulmonary neoplasms

I.	Epidermoid Carcinomas
II.	Small Cell Anaplastic Carcinomas
III.	Adenocarcinomas
	1. Bronchogenic
	a. acinar
	b. papillary with or without mucin formation
IV.	Large Cell Carcinomas
V.	Combined Epidermoid and Adenocarcinomas
VI.	Carcinoid Tumors
VII.	Bronchial Gland Tumors
	1. Cylindromas
	2. *Mucoepidermoid tumors*
VIII.	Papillary Tumors of the Surface Epithelium
IX.	Mixed Tumors and Carinosarcomas
X.	Sarcomas
XI.	Unclassified
XII.	Melanoma
XIII.	Mesotheliomas

SOURCE: Kreyberg, L. (22).

TABLE 3.—Histologic types of pulmonary cancers in smokers and nonsmokers

		Male		Female	
Type	Total	Smokers	Non-Smokers	Smokers	Non-Smokers
Epidermoid	992	892	7	80	13
Small Cell	640	533	4	100	3
Adenocarcinoma	760	492	39	128	101
Large Cell	466	389	16	46	15
Bronchioloalveolar	68	35	4	13	16
TOTAL	2,926	2,341	70	367	148

SOURCE: Resenow, E.C. (31).

Other centers have similar data, although the proportions by histologic type may vary with the pathologic criteria used, patient population, geographic location, and other factors.

Earlier epidemiologic studies suggested that cigarette smokers were more likely to develop squamous-cell and small-cell lung carcinoma than other types. However, more recent investigations indicate that all four major histologic types of lung cancer—including adenocarcinoma, which appears to be increasing rapidly in recent years—are related to cigarette smoking in both men and women (43).

In 1980, of the estimated 117,000 newly diagnosed cancers of the lung in the United States, 32,000 will be among women. There will be an estimated 25,500 deaths from lung cancer in women (1).

In 1950, women accounted for approximately 1 in 12 of all lung cancer deaths. By 1968 the proportion was 1 in 6; in 1979 women dying of lung cancer will represent over one-quarter of all lung cancer victims. White women have death rates from lung cancer which are similar to those of nonwhite women, while the rates of white males remain below those of nonwhite males. These differences may be due to differences in the smoking habits of blacks and whites described elsewhere in this report.

Many prospective studies have found that the lung cancer death rate for smokers was far in excess of the rates for nonsmokers in both sexes; as previously mentioned, the rates for male smokers dramatically exceeded the rates for female smokers. However, even the nonsmoking male had a higher incidence of, and death rate from, lung cancer than the nonsmoking female (9). This evidence suggested that women might have a decreased susceptibility to lung cancer. A more careful examination of the data indicates that most of the differences between male and female lung cancer rates can be explained by differences in smoking habits and occupational exposures.

As discussed in other sections of this report, a smaller percentage of women than men smoke and, when they do smoke, they are more likely to adopt smoking behaviors that have been shown to have a lower risk of developing lung cancer. That is, they smoke fewer cigarettes per day, inhale less, start smoking later in life, and are more likely to smoke low-tar and low-nicotine and filter cigarettes. In addition, it is important to consider the cohort effects on the differences in rates between males and females. Over 85 percent of those who smoke regularly began between the ages of 12 and 25 (29). Men first began to smoke in large numbers just before and during the First World War. As each succeeding birth cohort passed through the age of initiation (12 to 25), a larger percentage began smoking until the groups born between 1915 and 1930 were reached (17). In the birth cohorts born after 1930, fewer began to smoke regularly. The risk of developing lung cancer increases exponentially with age and duration of smoking, with the increase starting 15 to 20 years after the beginning of regular smoking. This accounts for the dramatic rise in the male lung cancer death rates noted in the 1930s. As those birth cohorts with higher smoking rates replaced those with lower smoking rates, the age-specific lung cancer rates rose steadily; and as each of the heavy-smoking birth cohorts grew older, their lung cancer risk

continued to accelerate, resulting in a very steep rise in the overall male lung cancer death rate. The overall cancer rates among men will continue to rise (albeit more slowly) as those birth cohorts with the heaviest smoking prevalence replace those with lower prevalence in the older age groups where the lung cancer death rates are the highest. As these birth cohorts with high smoking prevalence pass through the age groups and are replaced by birth cohorts with lower smoking prevalence, declines in lung cancer rates should be noted.

They should be noted first in the age-specific death rates for the younger age groups and later in the overall lung cancer death rates. The first indications of this change have been noted with a decline in the age-specific death rates in males born after 1930. It is therefore important to consider this cohort effect when examining the differences between lung cancer rates of men and women.

Women began to take up smoking in large numbers 20 to 30 years later than men (in the early 1940s). This rise in smoking prevalence was produced by predominantly young women first using tobacco as cigarettes. This is in contrast to the rise in men which included a substantial percentage of men of all ages who switched from other forms of tobacco use to cigarettes. The rise in lung cancer rates in women occurred as those cohorts with high smoking prevalence reached the ages where lung cancer occurs with significant frequency (age 45 and over). Since most of these women began smoking cigarettes prior to age 25 they would have at least 20 years of exposure by age 45 in contrast to the shorter durations of exposure at age 45 for those men who switched to cigarettes from other forms of tobacco around the time cigarettes first came into widespread use. This greater duration of exposure at any given age for women in these first heavy smoking birth cohorts compared to the first cohorts in men, should result in a more abrupt rise in lung cancer rates in women. This rapid rise in female lung cancer death rates began to be observed in the late 1950s. As birth cohorts with higher smoking prevalence continued to replace those with lower smoking prevalence, the rates rose steeply, reproducing the phenomenon noted in males 20 to 30 years earlier with some indication that the rise is even steeper for women. If one subtracts 25 years from the female cancer death rates in Figure 1, the rates for women are only slightly below the rates for men. This small difference is explained by lower prevalence of smoking and less hazardous smoking patterns of women and their less frequent exposure to occupational carcinogens. Thus, close scrutiny of the trends reveals no substantial protective effect for women on the risk of developing lung cancer but rather leads to a

TABLE 4.—Age-adjusted lung cancer mortality ratios—age began smoking and degree of inhalation

Age Began Smoking	Male	Female
15	16.8	2.5
15–19	14.7	5.0
20–24	10.1	3.4
25+	4.1	2.3
Depth of Inhalation	**Male**	**Female**
None	8.0	2.0
Slight	8.9	2.3
Moderate	13.1	3.5
Heavy	17.0	7.1

SOURCE: Hammond, E.C. (11).

TABLE 5.—Age-adjusted relative risks of lung cancer by number of cigarettes smoked

		Number of Cigarettes Smoked Daily			
		1–9	10–19	20–39	40+
ACS Study	Male	4.6	8.6	14.7	18.8
	Female	1.3	2.4	4.9	7.5
		1–14		15–24	25+
British Physicians	Male	7.8		12.7	25.1
	Female	1.3		6.4	29.7

SOURCE: Doll, R. (6,8), Hammond, E.C. (11).

sobering projection of a reproduction of the male lung cancer epidemic in women (Figure 1).

GEOGRAPHIC DIFFERENCES

Lung cancer death rates, including all histologic types, are highest in industrialized countries where there has been a higher smoking prevalence for a longer time. Women in Scotland have one of the highest death rates from lung cancer of women of any country. Their tobacco consumption per smoker approaches that of English and Welsh men (19). Current tobacco consumption by Scottish women is only a little lower than the consumption of Scottish men 20 years ago. In England and Scotland, where the upper socioeconomic classes have reduced their

TABLE 6.—Lung cancer mortality ratios for females by duration of smoking: Swedish study

Duration of Smoking in Years	Mortality Ratios
Nonsmokers	1.0
1–29 years	1.6
30+ years	9.6

SOURCE: Cederlof, R. (4).

cigarette consumption in recent decades, there is a significantly greater lung cancer mortality rate in the lower socioeconomic classes among women (19).

Age-adjusted death rates for lung cancer in women in select countries indicate that women in Hong Kong have the highest rates, while those in Scotland are second and those in England and Wales are third. The United States ranked sixth world wide (1).

Among nonsmokers, lung cancer is found slightly more often in urban than in rural areas; however, the marked increase in lung cancer among smokers in urban areas suggests that urban living exerts a potentiating rather than an additive effect on the incidence of lung cancer. Urban living has little independent effect on lung cancer induction in comparison with even modest smoking of filtered low-tar and low-nicotine cigarettes (5,10).

SMOKING PATTERNS AMONG WOMEN

Although women tend to have different patterns of smoking than men, the relative relationships between smoking and lung cancer are the same. Lung cancer rates for women who smoke increase with increased dosage as measured by several dosage measures, including number of cigarettes smoked per day, duration of smoking habit, degree of inhalation, age of initiation of smoking, and the "tar" and nicotine level of the cigarettes smoked. These data, obtained from several prospective investigations, are examined in Tables 4, 5, 6, 7, 9, and 10. The more cigarettes an individual smokes, the more likely that individual will die of lung cancer (Table 5). Overall, female cigarette smokers have 2.5 to 5.0 times greater likelihood of dying from lung cancer than nonsmokers (Table 7). As discussed earlier, when the full impact of the cohort effect is felt, this ratio will probably approach that for men (8 to 12).

Doll, et al. studied the cause-specific mortality experience among approximately 6,200 female physicians in England during

TABLE 7.—Lung cancer mortality prospective studies

		Age Adjusted Lung Cancer Death—Relative Risks	
		Nonsmokers	Cigarette Smokers
ACS	Male	1.0	10.1
	Female	1.0	2.6
British Physicians	Male	1.0	14.0
	Female	1.0	5.0
Swedish Study	Male	1.0	8.2
	Female	1.0	4.5

SOURCE: Cederlof, R. (4), Doll, R. (6,8), Hammond, E.C. (11).

the period 1951 to 1973 (6). The results of this study are presented in detail in Table 8, which also includes data from a previous report on male physicians (8).

It is apparent that smoking and lung cancer are similarly related in men and women. In both sexes, lung cancer mortality was at least three times as high in ever-smokers as in never-smokers, at least twice as high in current heavy smokers (more than 25 cigarettes) as in light smokers (less than 15 cigarettes), and exhibited a significant dose-response relationship. The magnitude of the smoking effect on lung cancer for females and males was approximately the same. The relative risks for mortality from lung cancer for moderate (15 to 24 cigarettes per day) and heavy (more than 25 cigarettes) smokers were 6.3 and 29.7 among females, and 10.6 and 22.4 for males.

The authors emphasize, however, that no conclusions can be drawn from this data about the magnitude of the biologic effects of smoking in men compared to women. Since the authors documented differences in lifetime smoke exposure (later age at initiation and lower prevalence of inhalation among females), lifetime smoking exposures between the sexes were not directly comparable. This issue will be resolved only when studies examine the effect of smoking in cohorts of women whose lifetime smoking behavior more closely matches that of the men to whom they are compared.

A number of retrospective studies have examined the relationship of smoking and lung cancer in women. The 1971 Health Consequences of Smoking reviewed many of these investigations and showed a smoker-to-nonsmoker risk ratio ranging from 0.2 to 6.8 for females. The reader is referred to this volume for a more detailed discussion of these studies. Results of these investigations reveal sex differentials similar to those found in

TABLE 8.—Death rates from lung cancer and smoking habit when last asked, British physicians 1951–1973

	Total Popul.	# Deaths	Annual Death Rate per 100,000 Persons Standardized for Age					X^2	
					Current Smokers—Dose Per Day			Nonsmokers vs. Others	Trend (Dose/ Response)
			Nonsmokers	Ex-Smokers	1–14	15–25	25+		
Women	6,194	27	7	23	9	45 (cigarettes only)	208	13.47*	61.59*
Men	34,440	441	10	43	52	106 (any tobacco/grams) (1 gram = 1 cigarette)	224	41.9*	197.04*

*($P < .001$)
SOURCE: Doll, R. (6,8).

TABLE 9.—Age-adjusted lung cancer mortality ratios* for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

*The mortality ratio for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.
SOURCE: Hammond, E.C. (11).

the larger prospective studies, with males having higher overall lung cancer rates compared to females. However, the lung cancer rates of smokers are significantly higher than those of nonsmokers for both sexes.

The women who smoke low-"tar", low-nicotine cigarettes have a lower age-adjusted lung cancer mortality rate than women who smoke high-"tar", high-nicotine cigarettes. Women who smoke medium-"tar", medium-nicotine cigarettes have mortality rates in between (12) (Table 9). However, even the low-"tar" and low-nicotine cigarette smoker has a rate substantially higher than the nonsmoker.

These data suggest some benefit from smoking low-"tar", low-nicotine cigarettes. However, a further comparison of women who smoked less than one pack of high-"tar", high-nicotine cigarettes daily with women who smoked more than one pack of low-"tar", low-nicotine cigarettes daily revealed that the smoker of more than a pack a day of low-"tar", low-nicotine cigarettes had over twice the age-adjusted lung cancer mortality rate of the woman who smoked fewer cigarettes, but with high "tar" and nicotine (Table 10).

In a retrospective study standardized for duration of smoking, number of cigarettes smoked, inhalation and butt length, long-term female smokers of filter cigarettes had a lower relative risk of developing cancer than smokers of non-filter cigarettes (46).

CESSATION OF SMOKING

Although the risk of developing lung cancer increases with age, both for smokers and nonsmokers alike, women in good health who quit smoking will, over a period of years, experience a reduction in their relative risk of developing lung cancer. About 15 years after they have quit smoking, the risk of developing lung cancer approximates that of the nonsmoker.

TABLE 10.—Age-adjusted lung cancer mortality ratios* for males and females, comparing those who smoked a few high tar and nicotine (T/N) cigarettes with those who smoked many low T/N cigarettes

	1–19 high T/N cigarettes/day	20–39 low T/N cigarettes/day
Males	1.00	1.6
Females	1.00	2.1

*The mortality ratio for the category with lowest risk was made 1.00 so the increase in risk with smoking more cigarettes/day could be illustrated.
SOURCE: Hammond, E.C. (11).

EXPERIMENTAL CARCINOGENESIS

Tobacco tars, tobacco smoke, and single or mixtures of chemicals found in tobacco smoke have been used with various species of animals in carcinogenesis experiments involving skin painting, subcutaneous injections, tracheobronchial implantation, and/or instillation and inhalation. Some experiments have reported sex differences in the occurrence of lung tumors following exposure to chromium oxide (26).

However, in a recent monograph on lung cancer, separate reviews on tobacco carcinogenesis, radiation carcinogenesis in the respiratory tract, and experimental models for studies of respiratory tract carcinogenesis did not yield information suggesting that the male lung of any of the species studied was more susceptible than the female lung to carcinogenic action by either tobacco products or radiation (16). The reader is referred to previous Smoking and Health Reports for summaries of experimental tobacco carcinogenesis studies.

Larynx

The larynx is a small, complex structure, which produces speech, controls the flow of air in and out of the lungs, and prevents aspiration during swallowing. In 1980 there will be an estimated 1,700 new cases of laryngeal cancer and 600 deaths from that tumor in U.S. women (Table 1). Laryngeal cancer has occurred predominantly in men, but more and more women are developing laryngeal cancer as their smoking and drinking habits come to approximate those of men. The male-to-female ratio for laryngeal cancer exceeds that of lung cancer. Laryngeal cancer occurs in the fifth, sixth, and seventh decades both in men and women. While the disease is uncommon, its incidence has continued to rise over the past quarter century,

especially in women, substantially because of changes in their smoking habits.

Cancer can occur either in the glottis (true cord, 70 percent of cases), or in the subglottic or supraglottic region (false cord, 25 percent of cases). Usually the neoplasm is epidermoid carcinoma when examined histologically. Since a tumor that interferes with speech gives rise to early symptoms, glottic cancers are usually diagnosed at an early stage and are curable in over 60 percent of the cases. When the tumor arises in the subglottic or supraglottic region, interference with phonation or speech may not occur as early as when neoplasm begins on the glottis. The tumor may, therefore, reach a greater size and be accompanied by significant local tissue invasion and destruction as well as metastasis. Patients with tumors discovered when they are still localized in the larynx have approximately an 80 percent cure rate, while advanced lesions have a 33 percent 5-year survival rate.

Laryngeal cancer displays a strong dose-response relationship with smoking, increasing with the number of cigarettes smoked per day, the "tar" and nicotine content of the cigarettes smoked, the depth of inhalation and number of years cigarettes were smoked. The risk of developing laryngeal cancer is inversely related to the age at which smoking began (43). A lower risk for laryngeal cancer has been demonstrated in women who used filtered cigarettes for 10 years or more compared to those who smoked non-filtered cigarettes. Nonetheless, the risk remained well in excess of that experienced by nonsmokers (45).

Excessive use of alcohol by nonsmokers also results in an increased incidence of laryngeal cancer. Heavy drinkers of alcohol—that is, greater than seven ounces of whiskey or its equivalent per day—who also smoke cigarettes have a greater risk of developing laryngeal cancer than if they either smoked or drank to excess alone. There is a synergistic effect of smoking and drinking on laryngeal cancer development (43,44).

When women quit smoking, their relative risk of developing laryngeal cancer decreases until 10 years after cessation when their risk approaches that of the nonsmoker (45).

A number of investigators have found an association between exposure to asbestos and the subsequent development of laryngeal carcinoma (43).

Oral

Oral neoplasms include cancer of the lip, tongue, gums, buccal mucosa, hard and soft palate, salivary glands, floor of the mouth, and oropharynx. In the United States for 1980, there

will be 17,900 new cases in men and 7,600 in women, resulting in 6,100 deaths in men and 2,700 deaths in women (1). While different histological types of cancer can occur in this group, squamous cell carcinoma is by far the most common, except for the tumors of the salivary glands. Five-year survival rates range from 25 percent in those patients whose tumor is advanced when first diagnosed to 67 percent for those whose tumor is localized at diagnosis.

In women, oral cancers account for 1.9 percent of all neoplasms, while they account for 4.7 percent of all cancer occurring in men. Deaths from the various oral cancers account for 1.4 percent of cancer deaths in women and 2.8 percent of all cancer deaths in men. Cigarette, pipe and/or cigar smoking are all associated with increased oral cancers. Heavy alcohol use (over 7 ounces per day) has been shown to be an independent causative factor (32,42). When both are used together by women or men, synergism results in an even greater incidence of oral cancer (3). Poor oral hygiene or inadequate dentition is also a risk factor (15).

Most of the prospective epidemiologic studies have concentrated on men. In Japan a large prospective study showed the mortality ratio for oral cancer to be 2.88 for the male cigarette smoker and 1.22 for the female cigarette smoker compared with the nonsmoker.

Leukoplakia or an abnormal thickening and keratinization of the oral mucous membrane is recognized as a precancerous condition. While found in the western world, it is most common in Asian countries where a mixture of tobacco and betel nut or lime ash chewing is common, and in those countries where reverse chutta (cigar) smoking occurs. Women in certain regions of India are more likely to engage in reverse chutta smoking than men, although both women and men develop carcinoma of the hard palate after years of reverse chutta smoking (30).

Women and men with mouth, pharynx, and larynx cancer who continue smoking after surgical treatment of the first neoplasm have a 40 percent probability of developing another neoplasm of the head and neck. Only 6 percent of the patients who quit smoking develop a second cancer in the region. Less than 10 percent of oral cancer patients are nonusers of tobacco; almost all have a well-differentiated carcinoma and a relatively high cure rate (23).

Esophagus

Carcinoma of the esophagus will be diagnosed in 6,200 men and 2,600 women in the United States in 1980 (1). The American Cancer Society estimates that there will be 5,500 deaths in men

and 2,100 deaths in women from this disease (1). Median survival time once esophageal carcinoma is diagnosed is 6 months. The 5-year survival rate is only 3 percent. Esophageal carcinoma rates have declined in the white population over the past 25 years. However, they have increased in the black population in both sexes. This may reflect genetic or environmental factors. In the Caspian littoral, there is a remarkable difference in esophageal carcinoma incidence in people of comparable background and socioeconomic status living only 400 kilometers apart. There is a 30-fold higher incidence in women living in the desert northwest section of Mazandran, Iran, compared with the fertile Caspian rainbelt 400 kilometers to the west (20).

Data from a number of retrospective studies show that smoking increases the risk of developing esophageal carcinoma. Neither the relative risk of developing esophageal carcinoma nor the steepness of the dose-response relationship with cigarette smoking is as great as it is for carcinoma of the lung or larynx (45). Individuals who stop smoking or switch to low-tar, low-nicotine cigarettes will, after a lag period, experience lower relative risks of developing esophageal carcinoma, although the fall-off is not as steep as with lung and laryngeal cancer. In the male, both retrospective and prospective studies show that pipe and cigar smokers have mortality rates from esophageal carcinoma similar to cigarette smokers. There are no prospective epidemiologic studies of female smokers in this country large enough to permit development of a mortality ratio comparison to nonsmoking females.

Ingestion of alcohol is also a major etiological factor in esophageal carcinoma. A dose-response relationship exists, with increasing alcohol ingestion resulting in an increased incidence of esophageal carcinoma. As in the larynx, synergism of the carcinogenic effect on the esophagus occurs with the use of both tobacco and alcohol (45). Whether or not nutritional deficiencies, which occur frequently with severe, chronic alcoholism, play a role in carcinogenesis remains unknown, as does the possible contribution of chronic iron deficiency found in Plummer Vinson's syndrome (Paterson-Kelly syndrome, sideropenic dysphagia).

Ninety-eight percent of esophageal cancers are histologically squamous cell in type. In an autopsy study, Auerbach found more abnormalities of the esophageal tissues—including atypical nuclei, disintegrated nuclei, hyperplasia and hyperactive esophageal glands—of tobacco smokers as compared with nonsmokers (2).

Esophageal carcinoma can be produced experimentally by both benz(a)pyrene and the nitrosamines. Both benz(a)pyrene

and a group of nitrosamines have been identified in tobacco smoke. The appearance of experimentally-produced squamous cell carcinomas can be accelerated by dissolving the carcinogen in alcohol, a laboratory experiment duplicated daily by thousands if not millions of our citizens (43).

Urinary Bladder

Cancer of the urinary bladder will occur in 26,000 men and 9,500 women in the United States during 1980 and it will kill 7,000 men and 3,300 women (1). Cancer of the urinary bladder is frequently multicentric in origin. If found while still localized in the bladder wall, the 5-year survival rate is 72 percent, in contrast to 14 percent for those patients whose disease had already spread when the diagnosis was first established (1).

Bladder cancer has been associated with occupational exposure to aniline dyes, leading to the study of aromatic amines as potential carcinogens. 2-Naphthylamine, xenylamine, benzidine, and 4-nitrobiphenyl have all been implicated (43).

Numerous retrospective studies have shown a relationship between smoking and urinary bladder carcinoma in both men and women (17). The likelihood of either women or men developing bladder cancer increases with the number of cigarettes smoked, the duration of smoking, and tar and nicotine content of the cigarette smoked. Changing to low-tar, low-nicotine cigarettes or more clearly, cessation of smoking, decreases the relative risk of developing bladder cancer. The risk of an ex-smoker developing urinary bladder cancer approaches that of the nonsmoker years after cessation (46).

In prospective studies in Japan and Sweden, women who smoke are 1.6 to 2.7 times as likely to develop bladder cancer as nonsmokers (3,14). In an international study of successive birth cohorts in the United States, United Kingdom, and Denmark, Hoover and Cole found increasing rates of bladder cancer associated with increased cigarette smoking in men and women in both suburban and rural areas and in all nationalities studied (17). It has been estimated that 30 percent of urinary bladder cancer in women can be attributed to cigarette smoking (43).

Kidney

Cancer of the kidney will occur in 10,500 men and 6,400 women in the United States during 1980 (1). Some 4,800 men and 3,100 women will die of renal carcinoma (1). The 5-year survival rate is between 40 and 50 percent (1). While the overall classification of kidney carcinoma includes tumors of the renal pelvis and